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MONITORING OF CREATINE KINASE LEVELS IN SPECIFIC MILITARY POPULATIONS FOR EARLY TREATMENT

by

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Table of Contents

List of Figures

List of Tables

Abstract

The high physical demand of military environments such as basic training, selection schools, and advanced courses subject the member to extreme muscle usage with potentially inadequate recovery time. As the muscle breaks down with extreme use, the protein, myoglobin, builds up in the blood. If the individual does not have sufficient rest time, allowing the body to recover, health problems can arise as the kidneys attempt to process the excess myoglobin. A blockage in the kidneys due to the protein can occur resulting in decreased function culminating in kidney failure and death if untreated. Extreme skeletal muscle breakdown that can result in kidney issues is rhabdomyolysis. Creatine kinase (CK) is an enzyme released by damaged muscle and is an accurate marker for muscle injury. Without CK monitoring, extreme muscle stiffness could be considered normal due to recent increase in physical activity. Determining a subset of military members that are at higher risk for extreme muscle damage can create a small population that would benefit the most from CK monitoring. Preexisting health conditions can increase an individual's susceptibility to rhabdomyolysis. The military allows a few of these preexisting health conditions upon entry while others are allowed after a member is on active duty. Monitoring this subset population during extreme exercise for CK levels can alert when proactive preventative action could prevent permanent damage.

INTRODUCTION

Overview of the Study

Military personnel often experience environmentally and physically extreme environments. This can push the physical limits of the individual. The very nature of competing for coveted jobs and hard selection courses further motivates personnel to physical extremes. In addition, the integration of new recruits from a wide range of backgrounds and states of physical fitness into a boot camp environment can represent a significant change in level of activity and muscle usage. While muscle soreness increases with additional use, extreme soreness can be indicative of a larger problem. Although not widespread, individuals with certain genetic traits and physical history can be more susceptible to exercise-related issues. This study will determine a susceptible population and the means of quickly identifying an exercise-related issue to help ensure prompt medical attention.

The Nature of the Problem

The high physical demand of military environments such as basic training, selection schools, and some courses subject the member to extreme muscle usage with potentially inadequate recovery time. As the muscle is broken down with extreme use, the protein myoglobin builds up in the blood. If the individual has inadequate time to recover and allow the kidneys to process the excess myoglobin problems can arise. A blockage in the kidneys due to the protein can occur, resulting in decreased function, culminating in kidney failure and death if untreated.[1] Creatine kinase (CK) is an enzyme released by damaged muscle and used as a marker for muscle injury. Without CK monitoring, recent physical activity allows one to excuse extreme muscle stiffness as normal. Another common indication of muscle injury is myoglobin

in urine resulting in a dark color. A trainee might be hesitant to report this condition for fear of removal from training. The problem is determining a subset of susceptible military members who would benefit from monitoring CK levels. This will help alert personnel when preventative action needs to occur before permanent damage results.

Purpose of the Study

The purpose of this study is to evaluate a subset of military members who could benefit from CK monitoring. Certain preexisting conditions, such as sickle cell trait and carnitine palmitoyltransferase deficiency, are not medically disqualifying conditions for military service[2] but could lead to a higher occurrence of issues post extreme exercise.[3] Other conditions such as compartment syndrome or a history of rhabdomyolysis are medically disqualifying upon service entry. These conditions are allowed, however, once on active duty unless further complications arise or a failure to preform duty occurs. Monitoring of CK levels for the population subsets described during extreme physical conditions could help prevent further complication and enable timely treatment to the member.

Research Question

The prevalence of extreme muscle breakdown is approximately 26,000 instances in the United States each year.[4] While this is not a high rate of occurrence, the nature of the military to engage in activities that result in extreme muscle breakdown creates a more susceptible military population. One instance of mass muscle breakdown occurred in 1971 with the hospitalization of a unit of 40 Marine recruits.[5] The research question this paper will answer is "what population of the military would benefit from monitoring creatine kinase levels during strenuous activity?" This research will seek to determine if the military contains a unique environment where members presenting with current health conditions could benefit from monitoring muscle

breakdown during high physically demanding conditions. The beginning argument is that CK levels should be monitored in specific military members during periods of strenuous activity. Extremely elevated CK levels can indicate impending decrease in kidney function or cardiac arrest that, if untreated, can result in death. Studies have shown a higher risk for elevated CK levels in sickle cell trait-positive recruits,[6] during extreme environment training, and those with a history of rhabdomyolysis[7] or compartment syndrome. Monitoring the CK level could alert to elevated levels before symptoms progress, allowing medical care to begin sooner and resulting in a faster recovery. Impacts on the individual's long-term health could also benefit. Current methods of monitoring CK levels involve blood draw and lab based assays costing resources, coordination and labor. Currently in development are faster, more portable methods of determining CK levels. Ideally, implementing novel testing methods with minimal training allows the option to monitor CK levels outside of a clinical setting.

Research Methodology

This study utilizes an evaluation research methodology. This will attempt to identify the need for limited CK monitoring and determine solutions using novel biomedical devices. Research efforts to date include a look at CK levels in injured war fighters,[8] CK level correlation to race and kidney failure in the military [9] and exertional rhabdomyolysis among military personnel.[10] The chance of exertional muscle damage is well documented in military recruits while the need of early diagnosis and management is clinically important.[11] The proposed research will contribute to the existing knowledge by incorporating recent methods of CK monitoring while reducing the population to test as it applies to the military. This research is applicable in physically demanding environments such as basic training or selection schools and

allows medical treatment sooner for those at a higher risk of kidney failure due to muscle damage benefiting both the individual and the military.

LITERATURE REVIEW

Muscle Injury

Muscle use that results in muscle injury creates various biological responses in the human body. This muscle injury results from a change in exercise regime especially in those not used to exercise. The typical soreness following muscular exertion is due to muscle breakdown. In small amounts, the body can handle slightly elevated myoglobin levels and all symptoms of soreness pass in just a few days. This is most common after an increase in muscle usage following a strenuous activity or a change in exercise routine. Issues can arise during extreme muscle usage. A new recruit going through basic training after a more sedentary life as a civilian is a prime candidate for muscle injury. Other examples such as an extended ruck march with a heavy pack or running a marathon without training can be a significant change in activity for an individual possibly resulting in muscle injury.

When the muscle undergoes prolonged use or a significant rise in activity level, the muscle breakdown results in the release of myoglobin protein, CK enzyme, potassium, phosphate and urate to enter blood circulation.[12] The excess myoglobin overwhelms the ability of the kidney to filter the protein and causes blockage of the renal tubules. This obstruction can result in kidney damage and failure if allowed to persist. Severe muscle breakdown is an acquired myopathy or acquired muscular pathologic condition. While preexisting health conditions allow a person to be more susceptible to severe muscle breakdown, there needs to be a catalyst such as a traumatic event or condition to cause the breakdown. In addition to exercise-

related muscle injury, other situations can result in muscle breakdown. Table 1 presents a comprehensive list of etiologies for conditions where extreme muscle injury can arise.

Table 1. **Exertional Causes of Rhabdomyolysis.**

Traumatic, Heat-Related, Ischemic and Exertional Causes of Rhabdomyolysis	
Lightning strike	Ischemic causes
Immobilization	Ischemic limb injury
Extensive third-degree burn	Exertional causes
Crush injury	Marathon running
Heat-related causes	Physical overexertion in untrained athletes
Heatstroke	Pathologic muscle exertion
Malignant hyperthermia	Heat dissipation impairment
Neuroleptic malignant syndrome	Physical overexertion in persons with sickle cell disease

Adapted from Sauret, John M., George Marinides, and Gordon K. Wang. "Rhabdomyolysis." American family physician 65, no. 5 (2002): 907-912.

Specific to a military environment are situations of prolonged confinement in one position, depleted blood supply to a muscle due to a binding or strap, blast and crush scenarios, physical and electrical shock, extreme physical exertion, heat dissipation impairment due to attire or environmental conditions, preexisting metabolic conditions, infection, electrolyte imbalance, and sickle cell positive trait individuals.[13]

Pathophysiology (Indications and Presentation of Condition)

Extreme muscle breakdown can present in a variety of ways depending on the person, underlying medical conditions and causation of the initial injury.[14] Initial observations include muscle tenderness, swelling and a feeling of muscle soreness. While this is common following exercise, additional indications such as dark colored urine signal renal distress. The dark color in the urine is a result of some myoglobin initially passing through the kidneys. Unfortunately, dark colored urine is not an infallible sign as urine production can cease or myoglobin can be

present at an insignificant amount to be visible.[15] This inconsistence of non-clinically observed symptoms can make it a challenge to identify skeletal myolysis (breakdown of muscle tissue).

Clinically, other indicators can be used to diagnosis severe skeletal myolysis although inconsistencies exist throughout the medical community on exact parameters. The initial presence of myoglobin in urine can be determined clinically via a urine dipstick test.[16] While this test actually tests for the presence of hemoglobin in urine, it will also react in the presence of myoglobin.[17] Specific myoglobin tests can take days to process, negating their usefulness in determination of skeletal myolysis.[18] Positive indication of myoglobinuria would directly relate to rhabdomyolysis as myoglobinuria is most commonly associated with rhabdomyolysis.[19] There is consensus that elevated CK levels above 20,000 U/L coupled with a muscular damaging event, muscle soreness, fever and malaise is a positive indication of rhabdomyolysis.[20]

Resulting Morbidity (Disease State)

Myolysis is the breakdown of muscle tissue while rhabdomyolysis specifically describes the breakdown of skeletal muscle. Rhabdomyolysis is specifically striated muscular muscle dissolution or disintegration.[21] Starting with the initial damage of the muscle, there are many subsequent events that cause further damage to the local muscle as well as allow an excess of proteins and elements into the bloodstream. While rest and intravenous fluids mitigate much of this damage, lack of proper medical attention will further the disease progression. The damaged muscle creates an influx of free calcium exasperated by the damage of the calcium regulating mechanism of a cell in the sarcoplasmic reticulum and mitochondria.[22] This calcium excess in turn causes further damage to the muscle resulting in fiber necrosis. The excess calcium also creates a pathologic state damaging the organelles of the cell releasing intracellular contents into the local extracellular environment near the muscle.[23] The release of intracellular contents

causes a positive feedback chain that sustains further muscle breakdown and eventually microvascular damage.[24]

If the microvascular damage is great enough to cause capillary leakage, the influx of fluid increases the local pressure around the muscle causing compartment syndrome. Compartment syndrome can develop in muscles confined by a matrix of connective tissue called fascia. Specifically, compartment syndrome occurs most often in the lower leg although it occasionally presents in the upper leg. The fascia creates a segregated compartment that is pressure isolated from neighboring muscle compartments. This excess pressure causes extreme pain and further muscle fiber necrosis. In fact, surgical intervention is required if the pressure of the compartment exceeds set standards.[25]

In addition to excess free calcium, an abundance of potassium also occurs. This potassium excess can result, although rarely, in severe hyperkalemia (high potassium). While the kidneys typically filter out excess calcium, acute renal failure from rhabdomyolysis can prevent this from taking place.[26] Hyperkalemia can disrupt the physiological electrical gradient that cells throughout the body rely on for normal function. This imbalance can result in changes in cardiac muscle function during repolarization causing cardiac arrhythmia.[27] Extreme cases of hyperkalemia, if left untreated, can result in cardiac arrest.

The most common serious complication of rhabdomyolysis is acute renal failure occurring in 15 percent of rhabdomyolysis patients.[28] Between crush and exertional muscle damage, rhabdomyolysis is a leading cause of renal failure.[29] Acute renal failure in the particular case of exertional muscle damage results by a combination hypovolemia/dehydration and aciduria.[30] Hypovolemia, commonly known as shock, is due to a decrease in blood volume. The decrease in blood volume presents in exertional situations as fluid builds up in the damaged

areas. As damaged muscle releases cellular contents into circulation, the kidneys filter these substances. A decrease in blood volume results in less blood supplied to the kidneys. Hypovolemia also results in less blood filtered through the kidneys leaving the muscular cellular contents in the circulation longer. The resulting blood state can result in aciduria, which is low urinary pH. This imbalance causes abnormal metabolic levels and can increase hyperkalemia.

Preexisting Health Factors

Several physiological conditions tend to be more susceptible to complications following severe muscle breakdown. Department of Defense Instruction 6130.03 *Medical Standards for Appointment, Enlistment, for Induction in the Military Services* outlines criteria for beginning military service and excludes many serious conditions that are not conducive with the mission and demands of the military. Other conditions can develop once an individual is a member of the military and are not necessarily cause for removal from service. Specific conditions, observed through multiple studies, result in a higher occurrence of rhabdomyolysis. It is these allowed conditions, either initially or once a military member, that are described in further detail.

The first condition allowed upon entry into military duty is sickle cell trait positive. Eight percent of individuals of African descent are sickle cell trait positive. Military population studies have reported 0.3 of 1,000 recruits are at risk of sudden death due to sickle cell trait induced conditions.[31] The risk of sickle cell trait related pathologies increases with age. Although, as of 2012, no reports of sickle cell trait related conditions have occurred beyond initial military training conditions.[32] Unfortunately, between 1977 and 2001, 26 exercise-related deaths occurred in sickle cell trait positive individuals during basic military training across all U.S. services.[33] Sickle cell trait is a phenotype expression that affects the shape of hemoglobin and can cause a sickle shape of hemoglobin. The irregular shape of hemoglobin can cause issues

with blood flow as well as cause multiple blood cells to "stick" together. Sickle cell trait is different from the more severe sickle cell disease. Sickle cell disease will exempt an individual from military service.[34] A person who is positive for the trait has one normal allele and one sickle cell allele while a person with sickle cell disease has two alleles for the condition. Both normal and sickle cell alleles are dominant resulting in a codominance expression for individuals with one allele of each. Sickle cell trait presents in varying ratios of normal and abnormally shaped hemoglobin. The ratio of the hemoglobin shape is pushed to favor an abnormal state under conditions of acidosis and hyperthermia.[35] Since acidosis and hyperthermia are also associated with exertional muscle breakdown, the sickle cell trait can result in an increase of abnormal hemoglobin during extreme exercise, further hindering circulation and kidney filtration. Training at high altitudes or high heat conditions are also risk factors for increased rhabdomyolysis for sickle cell trait individuals. Being aware of sickle cell trait and monitoring symptoms can help mitigate exertion caused pathologies and allow for faster treatment.

Another condition with a strong correlation to an increased risk of rhabdomyolysis following exercise is malignant hyperthermia. History of this condition will prevent entry to military service; however, this pharmacogenetic disease presents after exposure to anesthetic agents. Due to this specific interaction with anesthetic use, the condition can remain undetected upon entry to the military.[36] While anesthetic use will typically trigger malignant hyperthermia if present, this is not always the case. This condition occasionally presents in patients after exercise who previously had no complications following the use of anesthetics. One small sample size study reported 10 of 12 patients diagnosed with exertional rhabdomyolysis were also malignant hyperthermia susceptible.[37] Malignant hyperthermia is a genetic disorder that affects the gene that codes the channel in the sarcoplasmic reticulum that releases calcium. Since

myopathy disrupts the regulation of calcium, the presence of an abnormal calcium channel in the sarcoplasmic reticulum increases the already excess calcium level. Malignant hyperthermia typically presents with symptoms of muscle tightening, acidosis, fever and rapid heart rate.

Other genetic mutations that can increase susceptibility to rhabdomyolysis but do not prevent military service are several metabolic myopathies or muscular disease. DoDI 6130.03 lists several specific metabolic myopathies with the caveat that the list is not all-inclusive. The following unlisted metabolic myopathies could prevent service if they presented to an extreme where physical fitness standards could not be met. Carnitine palmitoyl transferase deficiency, myophosphorylase deficiency (McArdle disease), and adenosine monophosphate deaminase (AMPD) deficiency are all metabolic myopathies that have been positively correlated to an increased occurrence of rhabdomyolysis. These metabolic myopathies all involve a mutation in protein and enzyme mutations that can result in exercise intolerance to varying degrees. This exercise intolerance can lead to a faster myolysis condition that could quickly result in severe rhabdomyolysis necessitating prompt medical attention.

Compartment syndrome is another condition that can result in a higher susceptibility for rhabdomyolysis.[38] While described earlier as a resulting condition of extreme muscle use and the sequent muscle breakdown, compartment syndrome can present as either acute or chronic, and without other complications of muscle damage. Compartment syndrome is also prohibitive for entry to the military but allowed once in the military.[39] Chronic compartment syndrome presents typically in the lower leg after an aggravating exercise. Muscle stiffness and pain with certain muscle usage is common to chronic compartment syndrome. Since extreme muscle damage caused the compartment syndrome, argument follows that rhabdomyolysis could also result with further extreme muscle use. The pain associated with chronic compartment syndrome

often prevents extreme muscle use to the point of rhabdomyolysis. Surgery releasing the compartment pressure can relieve the pain and prevent future compartment syndrome.

Finally, a history of rhabdomyolysis is often associated with a higher chance of reoccurrence over an individual without the same history. This reoccurrence could be due to an underlying condition that caused the rhabdomyolysis in the first place.[40] History of rhabdomyolysis will bar an individual from entry to military service but does not guarantee removal once the member is in the military.[41]

EXERTIONAL MYOLYSIS PROBLEM

A physician, on an Antarctic expedition in 1912, noted increasing leg pain following daily hiking. This is the first documented exertional muscle necrosis. What is notable about the physician's observation is the lack of trauma accompanied by pain and bruising following a relatively typical activity.[42] Soldiers further correlated this account during the 1950s and 1960s with multiple published accounts of muscle necrosis following strenuous activity. The reported strenuous activity is similar marching with lack of a traumatic event. Substantial documentation exists for this combination of military and exertional muscle necrosis ranging from individual cases to entire basic training squadrons requiring hospitalization. The range of resulting morbidity and mortality is also as broad from an overnight stay in the hospital to death.

Statistical Data

Annually there are approximately 26,000 reported cases of exertional rhabdomyolysis throughout the United States.[43] Within the military population, the rate of exertional rhabdomyolysis is higher than the general population. Basic military training has the highest occurrence of rhabdomyolysis, both exertional and trauma-based. One military-based study in 2010, conducted by neurologists, used 5 years of Air Force basic military trainee hospital records

at Lackland Air Force Base. This study showed an occurrence of 22.2 cases of exertional rhabdomyolysis per 100,000 trainees. While this is a relatively low rate of occurrence, there are many studies of isolated instances of much higher rates of occurrence such as 39.2 percent [44] and 93 percent.[45] Exertional rhabdomyolysis accounted for 63 percent of all reported cases at the hospital serving the trainees during this period with 37 percent of the cases from trauma. Genetic and endocrine-based cases of rhabdomyolysis accounted for 9 percent of cases while toxin accounted for 23 percent.[46] This study showed that males with a higher body mass index (BMI) were at an increased risk of exertional rhabdomyolysis than their peers.[47] Renal failure (19.1 percent vs 34.2 percent), length of hospital stay (3.29 days vs 5.11 days) and mortality (0 deaths vs 2.6 deaths) was also less for exertional rhabdomyolysis than other causes respectively.[48] Notable about this study is the young population with a mean age of 20.4 years. Physical screening prior to joining the Air Force further narrowed the sample population.[49] One of the most comprehensive studies conducted across all military branches' basic military training related deaths from 1977 to 2001 found 199 non-traumatic deaths with 70 percent of the deaths attributed to exercise. Of these 139 exercise-related deaths, 46 were due to induced heat stroke and/or rhabdomyolysis.[50]

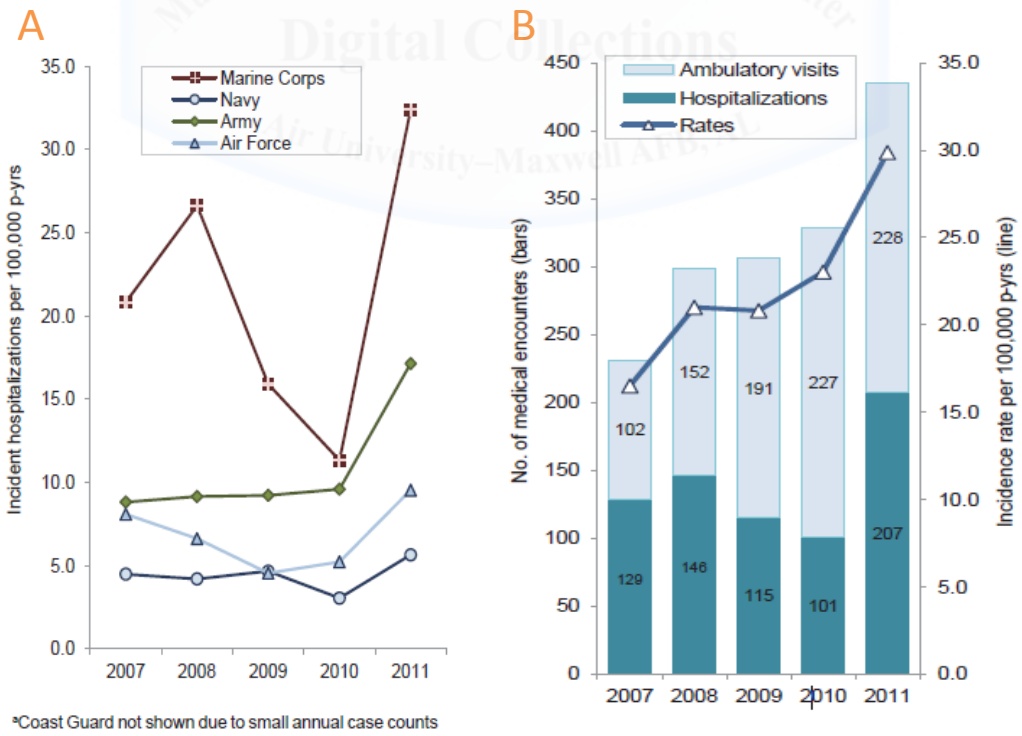
Throughout all of the studies included in this research, there is a notable lack of statistical evidence for higher exertional rhabdomyolysis during summer months. The Air Force trainee study at Lackland Air Force Base showed an almost equal occurrence during the summer months as during the winter months. One theory could be the vigilance the Air Force places on restricting strenuous exercise during periods of high heat. This same line of thought relates to pushing trainees more during winter months, assuming the cooler temperature reduces heat related incidents. Another study of U.S. Marine recruits showed a high occurrence of 39.2

percent of 337 recruits testing positive for myoglobinuria within the first 6 days of training during winter months.[51] This study occurred in the temperate climate of California where extreme cold was also not a factor. Though documented heat conditions do contribute to an increased likelihood of exertional rhabdomyolysis, the lack of correlating statistical data is most likely due to restrictions placed on activities during periods of high heat in a military setting.

Although there is an emphasis placed on basic military training and exercise-related muscle damage, the military as a whole has seen an upward trend from 2007 through 2011 for cases of exercise-related rhabdomyolysis.[52] The values in Table 2 include all cases of rhabdomyolysis across the military during the indicated period.

Table 2. Rates of Rhabdomyolysis

a) Exertional Rhabdomyolysis by service; b) rate of incidence per 100,000 people per year



Adapted from Costello, Amy, and Anthony Hawksworth. "MSMR." (2012).

Bases hosting major combat units saw the majority of rhabdomyolysis instances. This uptrend places importance on being able to quickly identify and get help to service members at risk of developing rhabdomyolysis. The increased emphasis of "functional fitness" at the base level encourages high repetition of movements in a CrossFit style approach to exercise. CrossFit, as an exercise construct, has numerous cases of rhabdomyolysis associated with it and is a known risk among the CrossFit community. The increase prevalence of this style of exercise could be contributing to the uptrend within the military as both "functional fitness" and CrossFit often attract the military and law enforcement populations.

This statistical data shows that there is a relevant amount of myolysis following strenuous exercise in various aspects of the military. While the majority of the cases originate in basic military training, there are a number of instances throughout the military. Narrowing down the population to specific activity combinations and preexisting health conditions can help to reduce the number of hospital days and occasional death. Having a capability to identify rhabdomyolysis in each of these cases could have reduced the amount of needed medical attention. The increasing trend of rhabdomyolysis occurrences across all service branches demonstrates this issue is progressively getting worse, necessitating attention.

High Incident Activities

Many activities found in the military directly relate to cases of extreme muscle injury. Highly repetitive movements, particularly those using larger muscle groups are prone to induce greater muscle injury. Basic military training can provide the correct combination of untrained personnel pushing their bodies to an extreme physical limit. The physical fitness of the individual directly relates to the possibility of extreme muscle injury, although athletes at a high level of fitness are not immune from exercise induced muscular damage. While typical basic

military training programing attempt to prevent overuse of muscle, there are examples of times where the training program exceeded muscle capacity with devastating results. Excessive repetitions of jump squats, push-ups, pull-ups, weighted ruck marches and endurance runs are common to reported cases of rhabdomyolysis and myoglobinuria. While the value of excessive exercise is difficult to define and varies for every individual, common values for extreme exercise seen in case studies shown in Table 3.

Table 3. High Occurrence Activities with Rhabdomyolysis Potential

Exercise	Amount*	Exercise	Amount*
push-ups	100	**ruck march**	15 miles
jump squats	80	**jumping jacks**	15-20 minutes
pull-ups	20	**sit ups**	100
leg raises	40 minutes	**thrusters**	15 minutes
running	varying miles		

***occurrences include multiple iterations of combinations of the above listed activities often multiple days in a row**

Adapted from Szczepanik, Michelle E., Yuval Heled, John Capacchione, William Campbell, Patricia Deuster, and Francis G. O'Connor. "Exertional rhabdomyolysis: identification and evaluation of the athlete at risk for recurrence." Current sports medicine reports 13, no. 2 (2014): 113-119.

Notable about this table is that occurrence of myoglobinuria followed by rhabdomyolysis necessitating hospitalization occurred after a combination of the listed exercises often preformed over multiple, consecutive days. The competitive nature of the military as individuals striving to do better than each other as well as their own previous attempts can push individuals into a myoglobinuria condition.

Beyond basic military training, selection courses can also push military members to physical extremes through excessive repetitions of exercises. In addition to repetitive exercise,

ruck marches can also be a candidate for inducing myoglobinuria and rhabdomyolysis. The multiple mile distance, extra weight of the ruck pack, and weather conditions can all combine to play a role in muscle deterioration. Less often seen, but still present, are cases of myolysis following lack of preparation for a physical fitness test. Unfortunately, one case resulted in the death of an Army member who pushed too hard during a physical fitness test after a year of relative inactivity. This Army member died of complications following myolysis including tachycardia and multisystem failure despite medical treatment.[53]

The wide range of physical activities and personnel conditions can create a daunting task of identifying those most at risk for myolysis. Combining activity with medical history of the individual can help narrow down candidates for myolysis monitoring.

Results of Myolysis Diagnosis in the Military

Cases of rhabdomyolysis across the military take a toll on both the individual and the military. The military member can experience extreme pain, muscle weakness, and range of motion limitation of the affected muscle group.[54] Beyond the initial pain, further complications previously described such as acute kidney failure can result in long-term physical damage to the patient. Resulting compartment syndrome can cause long-term pain for the patient and result in a physical profile until therapy or surgery is accomplished. Acute kidney failure can result in long-term kidney damage affecting the member's lifestyle. In extreme cases, death can result.

From the military perspective, rhabdomyolysis means removal or delay of training or duty for the member costing both medical resources and individual readiness. With an incident rate of 29.9 per 100,000 people per year,[55] and half of those requiring at least one night of hospitalization, the impact can be significant. The military's impact is through temporary loss of that member, hospitalization cost, lost work and/or recycling in training. Secondary impacts

include increased workload on other military members needed to help logistically with the patient and their family. Long-term complications such as compartment syndrome can take a member out of deployable status and necessitate ongoing physical therapy or surgery. Acute kidney failure, if severe, can result in military discharge.

Results of Early Myolysis Identification

Early identification of myolysis can allow recovery in a non-hospital setting in many cases. In one case, a 16-year-old recovered from myolysis caused by weight lifting without hospitalization. This patient had an initial civilian clinic visit but the physician sent him home with instructions for care. The patient recovered with rest, non-steroidal anti-inflammatory drugs (NSAIDs) and oral fluids.[56] There are many cases such as this of patients all ages and physical conditions who recovered with a similar regimen of outpatient treatment. Rhabdomyolysis alone will not cause death; however, resulting morbidities can lead to patient mortality. Early identification of myolysis can allow the patient to begin a recovery protocol and return to duty often without hospitalization.

Current Standard for Rhabdomyolysis Determination

One of the first indications for rhabdomyolysis is myoglobinuria. Directly related to rhabdomyolysis, myoglobinuria is a positive indicator for the condition.[57] The lack of sensitivity of urinary tests by not discriminate between myoglobin, hemoglobin and red blood cells diminishes the utility of this method.[58] While the presence of myoglobin in urine indicates rhabdomyolysis, hemoglobin or red blood cells are indicative of other issues. This test could then lead to an incorrect conclusion and delay needed care if hemoglobin was actually present. Although it is not always reliable, myoglobinuria is a simple indicator to signal the individual

that something is not right. Unfortunately, this should not be the only method of diagnosis particularly for individuals possessing an underlying condition who are prone to myolysis.

Creatine kinase is present in the blood stream following muscle injury. While a baseline value of CK is always present in circulation, excess CK is a positive indicator of rhabdomyolysis. Creatine kinase takes longer for the body to remove resulting in excessive levels being present for up to ten days.[59] High CK levels with recent physical exertion is the most sensitive as well as most convenient indicator for rhabdomyolysis.[60] The value that constitutes a high level of CK is debatable and varies by ethnicity. A study looking at CK levels in military recruits determined that greater than 50-times a normal level is consistent with rhabdomyolysis.[61] This same study looked at the fluctuation in CK levels throughout the first 14 days of U.S. Army basic military training. Following any exercise, a person will experience a rise in CK levels. The rise can be significantly greater than normal without any further complications than general muscle soreness. Multiple days of endurance work or strength conditions will further contribute to elevated CK levels that do not necessarily dictate a larger problem. The greater than 50-times normal marker demonstrated that even after 14 days of rigorous basic military training a healthy individual should not exceed that level. Military physicians confirmed this marker with a study of 499 basic military trainees where rhabdomyolysis did not occur with trainees approaching but not exceeding 50-times normal CK level.[62] The patient who exceeded the level and those who approached it showed that ethnicity plays a key role in baseline CK levels. If the study determined a baseline level for each individual, the member would remain under 50-times his or her normal level. This study concluded that a determination of a baseline CK level is necessary and varies with ethnicity. Table 4 shows a breakdown by ethnicity for baseline and after 7 days of basic military training.

Notable about this table is the entire population is male although there is no correlation for differing baseline CK between males and females.

Table 4. Comparison between Race and Serum Creatine Kinase (IU/L)

	Number	Baseline CK, mean/median (*P*-value)	Day 7 CK, mean/median (*P*-value)
African-American	27	664.4/371.5	2762.1/1548.0
Asian	8	351.0/247.5 (0.220)	1563.0/529.0 (0.141)
Caucasian	379	186.8/152.0 (<**0.001**)	1184.1/556.0 (<**0.001**)
Hispanic	57	260.4/153.0 (<**0.001**)	1070.0/536.0 (<**0.001**)
Native American	9	233.6/183.0 (**0.015**)	1006.5/961.5 (0.054)
Pacific Islander	15	171.3/118.0 (<**0.001**)	695.0/387.5 (<**0.001**)

P-values (two-tailed) are with are with respect to the log of serum CK, with all comparisons made vs. African-Americans. Bold = statistically significant at P < 0.05.

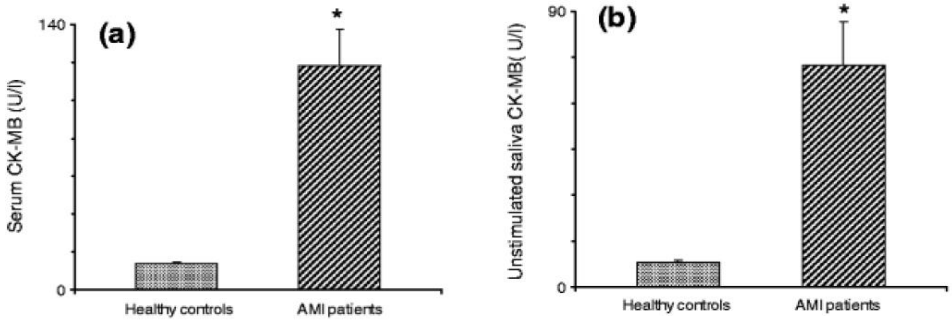
Adapted from Kenney, Kimbra, Mark E. Landau, Rodney S. Gonzalez, Julie Hundertmark, Karen O'Brien, and William W. Campbell. "Serum creatine kinase after exercise: drawing the line between physiological response and exertional rhabdomyolysis." Muscle & nerve 45, no. 3 (2012): 356-362.

Creatine kinase levels are currently determined in a laboratory or hospital setting through blood serum draw. While results can be determined within an hour, the test necessitates medical personal to remove the sample of blood as well as have a laboratory run a CK assay. This is difficult to accomplish in a remote setting with results delayed due to travel time. Further complicating collection is the need for a personalized CK baseline for each individual monitored. Monitoring change over time necessitates record keeping of results in addition to medical personnel as well as appropriate syringes and blood collection tubes. Due to the labor intensive and equipment-specific process combined with a low occurrence in a total population, it is simple to conclude that monitoring color of urine is enough of an indicator. While for a healthy military trainee this is enough, it is those more inclined to rhabdomyolysis where monitoring CK could truly be beneficial.

Novel Methods of Rhabdomyolysis Determination

Creatine kinase is a convenient marker for myolysis for many reasons. Myolysis broadly indicates muscle breakdown for all muscle types. Different types of CK relate to striated muscle (CK-MM) and cardiac muscle (CK-MB). CK-MB once considered a significant marker for cardiac necrosis and generated a significant amount of research to find rapid ways of measurement. In 2011, a group of researchers in Tehran, Iran developed a novel way to diagnosis myocardial infarction by monitoring the level of CK-MB in saliva.[63] CK-MB follows the same course as CK-MM as it enters the blood stream within a few hours of cardiac muscle injury and peaks approximately 24 hours post injury.[64] These results are significant and can potentially relate to CK-MM monitoring. Table 5 shows the results of CK-MB during a myocardial infarction as compared to CK-MB present in a control population of the same age and gender. Notable about this table is the serum CK-MB averages approximately 120 U/I while the saliva averages approximately 75 U/I.

Table 5 Concentration of CK-MB
(a) serum and (b) saliva for healthy control compared to acute myocardial infarction patients



Adapted from Mirzaii-Dizgah, Iraj, Seyed Fakhreddin Hejazi, Esmail Riahi, and Mohammad Mohsen Salehi. "Saliva-based creatine kinase MB measurement as a potential point-of-care testing for detection of myocardial infarction." Clinical oral investigations 16, no. 3 (2012): 775-779.

Striated and cardiac damaged muscle release CK-MM and CK-MB respectively into plasma. Plasma contributes to the contents of saliva so an increase in blood plasma CK-MM or CK-MB will be measurable in saliva.[65] The amount of CK in saliva is less as compared to blood plasma necessitating the determination of a new scale of acceptable and excessive levels. While in theory this method will work the same as it has for CK-MB, further testing could demonstrate the capability specifically for CK-MM. A saliva-based sample is cheap, portable and requires minimal training to operate. Medical personnel would not need to be present for sample acquisition although a laboratory would still analyze the sample. Fortunately, saliva is easy to store and transport, as it does not require the same refrigeration and handling care that blood samples necessitate.

Another method for monitoring CK in blood plasma is the innovative "lab on a chip" concept. While this concept has been in work for many years, recent technology enabling the miniaturization of key components has allowed this to be an up-and-coming option. This device uses a microneedle and switch with a sensor in a compact housing unit. Figure 1 provides illustration the glucose and cholesterol tested design.

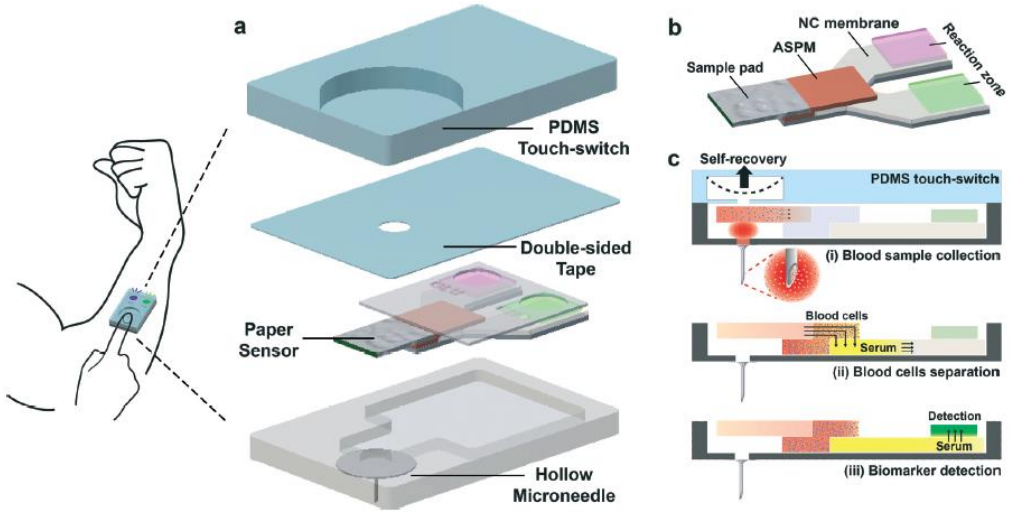


Figure 1. Blood Diagnostic System
(a) structure; (b) sensor diagram (c) sensor operating design [66]

Two separate biomarkers can be determined using this sensor. The initial experimental design tested for glucose and cholesterol but modifying this device would allow for detection of CK. The microneedle is double the diameter of a human hair (0.118 millimeters) and 1.6 millimeters in length.[67] This small size allows for almost pain free, small sample collection. The small size and colorimetric reading of results allow for portability and ease of use. Each device is single use necessitating enough of a supply for daily monitoring would need to be on hand. A minimally trained individual can do the tracking of results by comparing the color of the test to a provided key. Since the device confines the blood plasma specimen within the housing, chance of exposing others to biohazardous material is minimal. However, in a training environment or remote location, a sharps container is necessary to ensure proper disposal of the microneedle. The incorporated sensor eliminates the need for laboratory processing. The colorimetric assay and simple design could keep this a low cost, reliable method.

PROPOSED SOLUTIONS

Having established that military individuals with sickle cell trait, carnitine palmitoyltransferase deficiency, compartment syndrome or history of rhabdomyolysis are at increased risk for rhabdomyolysis, several solutions exist. These solutions monitor the military members with myolysis susceptible conditions and not necessarily a healthy individual. While healthy individuals can develop rhabdomyolysis, monitoring urine color and muscle fatigue typically allow ample warning to seek medical attention. All presented options need to have a baseline CK level taken before physical training commences. The military members with myolysis susceptible conditions, referenced throughout the options, are those individuals with sickle cell trait, carnitine palmitoyltransferase deficiency, compartment syndrome or history of rhabdomyolysis unless indicated otherwise.

Option 1: Lab-Based Monitoring

Currently there is no monitoring of CK levels at basic military training or during periods of increased rigorous training. However, the medical staff does alert trainees that they are to report dark colored urine. Occasionally, posters in the restrooms depict a color chart for normal and abnormal urine colors. Muscle fatigue and pain can bring a member to seek medical attention as well. Option 1 proposes a medical technician to draw samples from the targeted population at a set time each day throughout the training period. This could work for an on-base training environment where most days include dining facility visits three times daily. This easy solution would entail a fast detour for the individual to a table set up with a medic prior to a meal. Blood draw is quick and the on base laboratory analyzes the specimen. Since sickle cell trait positive and carnitine palmitoyltransferase deficiency can be present upon initial entry to active duty, the burden decreases at initial military training bases eliminating those with history of rhabdomyolysis and compartment syndrome. The low occurrence for both of these conditions (less than 1 in 1,000 individuals) results in a minimal impact of about 1 hour a day of one medical technician during initial military training. The minimal burden on the military combined with the potentially lifesaving monitoring to the individual creates an attractive option that can quickly be implemented. Bases housing initial military training are equipped with medical technicians and laboratory capabilities necessitating no increase in capability or training.

Option 2: Occasional Monitoring at Key Intervals

Another option that requires no additional base support or capabilities is to send the individual to the clinic daily during key periods of training. Examples of these periods would be during the first 2 weeks as well as any additional high physical intensity periods. While this does incur travel time for the individual from the training location to the on-base clinic, there is no

impact to the medical facility support staff. This is a viable option for a training base with reduced clinic manning that could not support a technician being away an hour or two as proposed in option one. Although the risk to the individual does increase as daily monitoring is not occurring. The key periods of intensified training would also need an additional day of monitoring after culmination as symptoms can take 24 hours to present. This option is more comprehensive than monitoring of urine color for at-risk individuals and may provide the needed warning before reaching a life-threatening condition.

Option 3: Daily Monitoring using Saliva Sensor with Laboratory

The next option incorporates the novel saliva-based sensor. This method is ideal for ease of sample collection and transportation. Saliva can easily be stored for pick up or delivery to the lab at a set time each day. Sample acquisition does not require additional personnel and minimal training is necessary. However, this sensor requires an additional study applying its usage to CK-MM. Fortunately, the similarity of CK-MB and CK-MM requires minimal, if any, modifications to the current design.

Option 4: Daily Monitoring using Remote Sensor without Laboratory

The last option of incorporating the "lab on a chip" method of portable biosensor could provide monitoring of the myolysis susceptible population with minimal pain, inconvenience and potentially governmental cost. This remote sensor could allow the individual to track their own CK level daily with minimal training on usage. No additional base medical personnel support is necessary although cost of the sensors is a factor to consider. Daily monitoring could provide the needed indication to the individual at risk to seek medical attention. Additional implementation of this device can occur in training courses beyond initial military training where laboratory equipment is not easily accessible. Deployed personnel might also benefit from this

device if long ruck marches and physical activity occurs. The popularity for a similar glucose sensor could drive down cost of this device and increase research for additional uses such as CK. Unfortunately, availability of the sensor for use with patients is unknown without funding additional research and testing.

CONCLUSION

Myolysis has a long history with the military and individuals pushing the limits of their physical capability. The military has not seen documented, rhabdomyolysis related hospitalizations of entire units since the 1970s but it is still an issue for individuals. The medical selectivity of the military helps eliminate a large number of health issues that need monitoring giving an impression of a remaining population capable of reaching physical limits without consequences. While this is the case of the majority of the initial military population, those with sickle cell trait positive and to a lesser extent carnitine palmitoyltransferase deficiency potentially experience a critical health condition if not monitored. Low cost changes, implemented when necessary, could provide a preventative measure benefiting both the individual and the military.

This research demonstrates the importance of monitoring for rhabdomyolysis condition though discussion of historical instances and the increasing trend of rhabdomyolysis occurrence across the military. Monitoring CK levels specifically provides a documented, accurate marker for level of myolysis. Limiting the monitored military population to those with history of at risk conditions during times of high physical activity allows the most susceptible members to receive the greatest benefit. The targeted populations identified and case studies presented provide a full picture of the situation. Recognizing signs of impending rhabdomyolysis can insure faster treatment resulting in lower hospital costs and faster return to duty status. The four conditions

described include analysis and supporting data for higher instances of severe myolysis. Monitoring these populations during high physical activity could help prevent a myolysis health emergency. Although the population of military members who qualify with these conditions is low, monitoring could reduce the impact of training to their personnel health. Unfortunately, cost of the two novel proposed solutions is not currently available. However, this cost should be less than the cost of long-term health issue and hospitalization.

RECOMMENDATION

The recommendation presented in this paper is multi-tiered. Initially, health care providers should begin collection of serum samples from the targeted population at initial military training then again at times of high physical activity. This could offer the lowest impact solution potentially benefiting all involved. Next, once available on the commercial market, incorporate the saliva sensor or "lab on a chip" monitoring method. Implementation of either of these methods could further lessen the impact to military training and the military members at a minimal coast to the military installation. Ultimately, both the individual military member and the military as a whole could benefit from reduced acute and chronic health issues as well as health care impacts through early identification of myolysis.

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